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## Alzheimer's Disease: A Hypothesis

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### Abstract

This hypothesis explores Alzheimer's Disease (AD) from a new perspective. It has been widely observed that AD patients present initially with "recent" memory loss. Recent memories are constantly created and updated, in contrast to "archived" memories, which do not require updating and which AD patients retain longer. Notably, memory creation and updating require the production and synthesis of proteins in neurons; and in AD patients, neurodegeneration is relative to the number of new proteins that the patient has synthesized. In neuronal protein synthesis, DNA transcribes mRNA, which is then translated into proteins in the cytoplasm.

During this process, the unzipped DNA double helix is vulnerable to assault and can subsequently enter apoptosis if it is unable to repair itself. A healthy individual can create and update memories without neurodegeneration, and even among dementia patients, not every protein synthesis is subject to assault or neuronal damage. However, the more proteins are synthesized, the greater the probability of assault. I propose here that, consistent with AD being an age-related disease, AD patients' immune systems have declined to the point where they are unable to eradicate assault agents and to repair DNA damage sustained from assaults during neuronal protein synthesis.

**Keywords:** Alzheimer's disease; Alzheimer's disease hypothesis; Protein synthesis; Neurodegeneration; Huntington's disease

### Introduction

Alzheimer's Disease (AD) is a form of dementia that occurs in older adults and whose treatment imposes a heavy burden on caregivers and societies. Nearly every proposed therapy for AD has failed in clinical trials. The alternative hypothesis suggested here explores AD based on observable traits exhibited in AD patients, presents a logical rationale, and is testable.

### Human memory is analogous to computer memory

It may be helpful to understand human memory as being functionally analogous to computer memory processes. Human memories of recent events are formed and stored in the hippocampus. By definition, due to their time-related nature, memories stored as "recent" must therefore be continuously changed and updated. Recent memories are thus comparable to "read-write" memory in computers, which retrieves and stores new information. In contrast, "archived" human memories refer to events that occurred a long time ago (long-term memories [LTM]); once stored, they remain largely unchanged. Archived memories are thus comparable to "read-only" computer memory.

### Memory loss relates to changes in memory contents

Recent memories are the first to be lost in AD patients [1]; in contrast, archived memories are retained the longest. For example, archived memories encompass things such as music heard a long time ago, and it has been notably observed that patients with AD often recognize familiar music [2]. The initial loss of AD patients' recent memories, paired with their longer retention of archived memories, leads to a suggestion that memories which require more updating are more likely to be lost in AD patients.

### Memory loss relates to protein synthesis in neurons

Neurons must create proteins in order to create, change, and store new memories [3,4]. Consequently, the addition and replacement of recent memories require the creation of more proteins than the comparatively simple continued storage of archived memories. It has also been observed that among AD patients, hippocampal memory neurons exhibit greater degeneration than neurons in "read-only" memory. Since these hippocampal neurons are responsible for continuously updating recent memories and must therefore continuously synthesize new proteins, it is plausible that neurodegeneration is related to the amount of protein synthesis required.

Another example of a neurodegenerative disease related to the amount of protein synthesis is Huntington's Disease (HD).

In HD, patient genomes have excessive copies of the repeat CAG segment. These genes code the protein glutamine, and HD patients thus make more of these proteins than is normal. Consequently, HD patients exhibit increased neurodegeneration [5]. Taken together, these observations point to neurodegeneration being proportional to the amount of proteins made by neurons in dementia patients.

### Viruses may be linked to Alzheimer's Disease

AD patient pathology has shown some evidence of a potential link to viral activity [6]. For example, one study found that viruses are more common in the brains of people with AD [7], while another study found that people who were treated aggressively with antiviral drugs for severe herpes infections had a ten-fold reduction in their relative risk of dementia [8]. Other studies have suggested that viruses can trigger psychiatric disorders [9].

## Literature Review

### A new Alzheimer's disease hypothesis

We know that recent memories are the first to deteriorate in AD patients, but we do not know precisely why. One possible answer relates to the previously established facts that a) neurons must synthesize proteins to create and update memories, and b) recent memories require many content updates. I thus hypothesize that neurons are subject to a higher risk of damage while synthesizing proteins. Since archived memories do not require much updating and consequently do not require as much protein synthesis, this would explain their comparatively reduced risk of degeneration in AD patients.

According to this hypothesis, it is necessary to explore why neurons might be damaged during protein synthesis. In mammalian protein synthesis, DNA unzips its double helix to transcribe a message into mRNA, which in turn is translated into proteins in the cytoplasm. The unzipped and re-zipped DNA double helix is in a vulnerable position. Assaults on nuclear DNA that occur during protein synthesis can thus damage the DNA, leading to genome instability and apoptosis. Moreover, it has been previously observed that a significant number of hippocampal and basal forebrain neurons in AD patients have been fully or partially replicated before apoptosis [10], suggesting that the neurons were unable to repair DNA errors and that the neurons were struggling prior to apoptosis.

My hypothesis thus hinges on the fact that memory creation requires neuronal protein synthesis [3,4] and can be briefly stated as follows:

*"Neurodegeneration in AD patients is caused by assaults on neuronal DNA during the protein synthesis required for memory creation".*

## Discussion

### Memory creation and storage relate to protein synthesis

According to the *de novo* protein synthesis theory of memory formation, LTM is understood to be stored in the brain as changes in synaptic connections [11]. For example, one study found that the creation of LTM requires new protein synthesis to stabilize learning-induced synaptic changes in the brain, although it remains unclear how the brain consolidates early labile memory into LTM [12]. Another study found that memory-encoding synapses have to be strengthened further to hold a memory in place, and that strengthening these synapses involves making new *Lypla 1* proteins (in conjunction with the degradation of *MOV10* proteins) [13].

Furthermore, a study of motor and sensory neurons suggested that LTM seems to persist covertly in cell bodies, after the pharmacological elimination of synapses that had been produced only after learning had occurred. The non-synapse memory must therefore have persisted inside the neurons themselves, indicating that LTM storage and synaptic change can be dissociated [14]. Similarly, recent neuroscience research has provided the first tentative neurobiological evidence for cognitive scientists' doubts about synapses as the (sole) loci of memories in the brain, suggesting a need for novel ways of thinking about the role of synaptic plasticity in learning and memory. Given that memory is so fundamental to a Turing machine, memory ought to be a function of individual neurons, not of the connections between them [15]. Another recent study has therefore proposed that consciousness may depend on biologically "orchestrated" coherent quantum processes in collections of "microtubules" within brain neurons, where microtubules are self-assembled from peanut-shaped "tubulin" proteins [16].

Regardless of the competing details of all of these hypotheses, they all suggest that proteins are required to create and store memories. This leads to the suggestion that AD-related neurodegeneration may occur during protein synthesis.

### Alzheimer's disease is an age-related disease

The tight junction of the blood-brain barrier (BBB) and good immunity work well so long as humans are healthy. Healthy persons can thus create and update many memories without exhibiting neurodegeneration. Moreover, even among the AD patients, not every instance of protein synthesis is subject to neuronal assault or damage. However, the more proteins are synthesized, the greater the probability of assault and thus damage. Further evidence of this hypothesis is provided by the finding that the histone protein H4K16ac is decreased in AD patients compared to similarly-aged persons without AD; H4K16ac regulates the compaction of chromosomes in the nucleus [17]. It has also been noted that early onset AD can be detected by the leaking of the BBB [18].

It may also be instructive to look at other examples of neurodegenerative diseases of the central nervous system (CNS). For instance, HD patient genomes have more CAG repeats and therefore synthesize more proteins. Since HD patients (like AD patients, despite the different mechanisms) synthesize more proteins than neurotypical persons, HD patients are thus subject to a higher probability of neuronal assault during protein synthesis. The different mechanisms behind the excessive protein synthesis help to explain why HD typically develops in middle age or even childhood, while AD is an age-related disease that typically develops in older adults. In HD patients, misfolded proteins are accumulated [19,20]. Moreover, the CAG repeat tract can be precisely excised from the Huntington gene by Cas9 nickase, thus reducing protein synthesis and providing an attractive treatment tool for HD [21]. In contrast, among AD patients the failure to successfully synthesize proteins is related to age rather than a faulty genome repetition: as humans age, the immune system declines and has less capacity to eradicate assault agents and to repair any DNA damage sustained from assaults during protein synthesis.

## Competing hypotheses

Other hypotheses regarding AD dementia have been proposed. One prominent hypothesis states that neurodegeneration is caused by toxins such as amyloid  $\beta$ -peptide or tau proteins. Billions of dollars have been spent on research based on this hypothesis, but to date no successful results have materialized in clinical trials. Diseases are often subject to multiple impacting factors, and therapies which target a minor impacting factor may succeed in the laboratory yet fail in clinical trials where only therapies targeting major impacting factors can achieve results; this plausibly explains the conflicting results of this hypothesis's laboratory and clinical trials.

Another hypothesis relates to mitochondrial dysfunction. Protein synthesis requires energy input, and it is possible that neurons are damaged by reactive oxygen species (ROS). Mitochondria are the major source of cellular ROS, so mitochondrial dysfunction is a plausible cause of excess ROS [22]. However, no trials of this hypothesis are foreseeable in the near future.

The present hypothesis proposes that AD neurodegeneration is caused by neuronal apoptosis due to DNA damage during protein synthesis. To summarize, based on the observed patterns of memory loss of recent and archived memories in AD patients, and the known fact that memory creation requires neuronal protein synthesis [3,4], the present hypothesis proposes the following four connected points:

- Memory loss in AD is relative to the number of additions and changes to recent memories.
- Memory loss in AD is thus relative to the quantity of proteins needed.
- Neurodegeneration in AD is thus relative to the amount of protein synthesis.

- Neurodegeneration and neuronal apoptosis in AD occur as a result of assaults during mRNA transcription, during which process the DNA double helix is unzipped and thus in a vulnerable state.

Although many different causes of this damage are imaginable, it seems most likely that viruses are the primary assault agents, particularly given the previously noted connection between increased viral activity and AD. Moreover, this hypothesis is testable.

## Testing the AD hypothesis

It is possible to carry out sequential trials to prove or disprove the present hypothesis, using the following methods:

### 1. Experimental mice are separated into three groups, A, B, and C.

- Group A is a control group
- Inject viruses into groups B and C
- Increase the BBB permeability of group C by applying an ultrasonic wave [23-25]; this enables viruses to enter the CNS

If AD (group C) > AD (group B) > AD (group A), this would suggest that viruses could be assaulting neurons in AD.

### 2. Split group C from Trial 1 into groups D and E, which may exhibit features consistent with the onset of AD.

- Group D is the control group.
- Apply antiviral therapy to group E; obtain blood samples to make sure that the viruses have been eradicated from the body.
- Apply an ultrasonic wave to increase BBB permeability and re-apply the antiviral drug to group E.

If AD (group D) > AD (group E), this demonstrates proof of the concept that it is possible to slow AD progression using viral therapy.

Alternatively, neurons can be placed into two separate dishes, X and Y, where X is free of viruses and Y is contaminated with viruses. Both groups will be induced to synthesize proteins by changing memory states. If group Y exhibits neurodegeneration and group X does not, this will suggest that viruses can assault neuronal DNA during protein synthesis.

## Conclusion

It is well known that as humans age, the immune system declines, and that AD is an age-related disease. It has also been widely observed that in AD patients, recent memories are lost initially while archived memories are retained longer. It is furthermore known that memory creation requires that neurons make proteins. However, this protein synthesis process leaves neurons vulnerable to assault, by viruses or other agents. Neurodegeneration in AD patients is thus plausibly due to assaults on neuronal DNA during protein synthesis.

## Conflicts of Interest

The author has no conflicts of interest to report.

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